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October 11, 2000

Docket Management Branch
Food and Drug Administration
Room 1-23 (HFA-305)
12420 Parklawn Drive
Rockville, MD 20857

Re: Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products [Docket No. 97N-484R]; Suitability Determination for Donors of Human Cellular and Tissue-Based Products [Docket No. 97N-484S]

Dear Sir or Madam:

On behalf of our client, Bio-Tissue, Inc., enclosed please find two copies of Comments in response to the above-referenced proposed rules. Please file them with the dockets for review.

If you have any questions, please contact me at (202) 414-9209.

Sincerely,

David J. Bloch, Esq.

cc: Scheffer Tseng, M.D., Ph.D.

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COMMENTS OF BIO-TISSUE, INC.
TO THE
U.S. FOOD AND DRUG ADMINISTRATION
ON
ESTABLISHMENT REGISTRATION AND LISTING FOR MANUFACTURERS OF HUMAN CELLULAR AND TISSUE-BASED PRODUCTS [DOCKET NO. 97N-484R]; SUITABILITY DETERMINATION FOR DONORS OF HUMAN CELLULAR AND TISSUE-BASED PRODUCTS [DOCKET NO. 97N-484S]

October 11, 2000

Bio-Tissue, Inc. respectfully submits these comments in response to the above referenced proposed rules, which appeared in the *Federal Register* on May 14, 1998 and September 30, 1999, respectively. Bio-Tissue urges the Food and Drug Administration (FDA) to clarify its interpretation of the term "homologous use" for purposes of regulating tissue products, and to state explicitly that the use of amniotic membrane in transplantation for use in corneal and conjunctival surface reconstruction is a homologous use. This clarification could be contained in the preamble, the discussion of comments received, or in the rule itself. While these comments are submitted following the close of the formal comment period, FDA has stated that comments received prior to completion of the final rule would be fully considered.

I. Product and Company Background

A. History of Bio-Tissue

Bio-Tissue was founded in April 1997, and has operated since July 1997 as a tissue bank supplying preserved human amniotic membranes. As a tissue bank, Bio-Tissue processes, stores and distributes each amniotic membrane it recovers in a manner that does not alter, expand or otherwise manipulate the tissue or any of its components. Bio-Tissue delivers to the end user the tissue it has preserved in the state in which it was received. Bio-Tissue's procedures for processing amniotic membranes are consistent with the criteria established by the American Association of Tissue Banks (AATB). Bio-Tissue has been granted a license by the State of New York Department of Health, Division of Laboratory Quality Certification. It is currently undergoing the process to obtain AATB certification.

Bio-Tissue believes that a substantial number of the membranes it distributes are acquired by or on behalf of ophthalmic surgeons for use in corneal and conjunctival

surface reconstruction (hereinafter "ocular surface reconstruction"). Since 1940, scientists have recognized the potential utility of amniotic membranes in conjunctival reconstruction.[1] Advances in the recovery and storage of amniotic membrane have improved the ability of surgeons to successfully transplant it to the ocular surface. Its utility for ophthalmic uses was reintroduced in 1995.[2]

B. Characteristics of the Amniotic Membrane

Amniotic membrane, the innermost layer of fetal (or placental) membrane, consists of a thick basement membrane and an avascular stroma. Its function is to protect the fetus from unwanted maternal insults during development. It is believed that this protective function is inherent to the unique properties of the membrane

The basement membrane facilitates migration of epithelial cells, reinforces adhesion of basal epithelial cells, and promotes epithelial differentiation.[3] The basement membrane is also important in preventing epithelial apoptosis.[4] Scarless repair of the membrane has been demonstrated in numerous models of fetal integumentary wound healing. The response to wounding is characterized by a rapid restoration of tissue architecture without an acute inflammatory reaction and with a limited, highly ordered deposition of collagen fibers to fill the defect. In other words, the membrane facilitates healing and regeneration of cells with a minimum of inflammation.

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[1] de RotthA. Plastic repair of conjunctival defects with fetal membrane. *Arch. Ophthalmol.* 1940;23:522-5.

[2] Kim JC, Tseng SCG. Transplantation of preserved human amniotic membrane for surface reconstruction in severely damaged rabbit corneas. *Cornea.* 1995;14:473-84.

[3] *See* Terranova VP, Lyall RM. Chemotaxis of human gingival epithelial cells to laminin: a mechanism for epithelial cell apical migration. *J Periodontol* 1986;57:311-317; Khodadoust AA, Silverstein AM, Kenyon KR, Dowling JE. Adhesion of regenerating corneal epithelium: the role of basement membrane. *Am J Ophthalmol* 1968;65:339-348; Sonnenberg A, Calafat J, Janssen H, et al. Integrin a6/b4 complex is located in hemidesmosomes, suggesting a major role in epidermal cell-basement membrane adhesion. *J Cell Biol* 1991;113:907-917; Guo M, Grinnell F. Basement membrane and human epidermal differentiation in vitro. *J Invest Dermatol* 1989;93:372-378; Streuli CH, Bailey N, Bissell MJ. Control of mammary epithelial differentiation: basement membrane induces tissue-specific gene expression in the absence of cell-cell interaction and morphological polarity. *J Cell Biol* 1991;115:1383-1395; Kurpakus MA, Stock EL, Jones JCR. The role of the basement membrane in differential expression of keratin proteins in epithelial cells. *Dev Biol* 1992;150:243-255; Barcellos-Hoff MH, Aggeler J, Ram TG, Bissell MJ. Functional differentiation and alveolar morphogenesis of primary mammary cultures on reconstituted basement membrane. *Development* 1989;105:223-235.

[4] Boudreau N, Sympson CJ, Werb Z, Bissell MJ. Suppression of ICE and apoptosis in mammary epithelial cells by extracellular matrix. *Science* 1995,267:891-893; Boudreau N, Werb Z, Bissell MJ. Suppression of apoptosis by basement membrane requires three-dimensional tissue organization and withdrawal from the cell cycle. *Proc Natl Acad Sci U S A* 1996;93:3500-3513.

C. Transplantation of the Amniotic Membrane to the Ocular Surface

The cornea of the eye is covered by an outer epithelial layer. When this epithelial layer is injured -- from infection, disease or trauma -- healing is accompanied by conjunctival epithelial ingrowth, neovascularization, chronic inflammation, and recurrent or persistent corneal epithelial defects. Collectively, these conditions are referred to as limbal (stem cell) deficiency.

Published research has demonstrated that amniotic membrane transplantation can be used to reconstruct the ocular surface when the cornea or conjunctiva is damaged. The amniotic membrane tissue appears to reduce the adverse effects associated with limbal (stem cell) deficiency. Observed effects following amniotic membrane transplantation include rapid epithelialization, return of normal epithelial phenotype, as well as reduction in inflammation, vascularization, and scarring.[5] These findings are consistent with the function that the amniotic membrane performs in utero -- *i.e.*, rapid restoration of epithelium, with a minimum of inflammatory reaction.[6]

Moreover, there appears to be a structural basis for these similarities of functional activity. A recent study showed that the structural components of the basement membrane of the amniotic tissue are very similar to those of the cornea and the conjunctiva.[7] The basement membrane of the amniotic tissue consists primarily of type IV collagen, laminin, and type VII collagen. Research demonstrated that the distribution of laminin and type VII collagen appeared to be the same in the basement membrane of the amniotic tissue, the cornea and the conjunctiva. In addition, the distribution of type IV collagen in the basement membrane of the amniotic tissue is

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[5] *See, e.g.*, Tseng SCG, Prabhasawat P, Barton K, Gray T, Meller D. Amniotic membrane transplantation with or without limbal allografts for corneal surface reconstruction in patients with limbal stem cell deficiency. *Arch. Ophthalmol.* 1998;116:431-41; Lee S-H, Tseng SCG. Amniotic membrane transplantation for persistent epithelial defects with ulceration. *Am. J. Ophthalmol.* 1997;123:303-12; Taylor, R. J. and Wang, M. X. Rate of re-epithelialization following amniotic membrane transplantation. Invest. *Ophthalmol. Vis. Sci.* 39, S1038. 1998; Azuara-Blanco, A., Pillai, C. T., Sarhan, A., and Dua, H. S. Amniotic membrane transplantation for ocular surface reconstruction. *Invest. Ophthalmol. Vis. Sci.* 39, S428. 1998.

[6] These same characteristics also suggest that amniotic membrane could be used to reconstruct damaged surfaces on the rest of the body, *e.g.*, the skin, the oral cavity, the surface of the digestive tracts, the surface of the urogenital tracts, the surface of the respiratory tract, the lining surface of the abdominal cavity, the chest and the heart.

[7] Fukuda K, Chikama T, Nakamura M, Nishida T . Differential distribution of subchains of the basement membrane components type IV collagen and laminin among the amniotic membrane, cornea, and conjunctiva. *Cornea.* 1999;18:73-79.

similar to its distribution in the conjunctiva. These similarities are consistent with the understanding that the basement membrane of the amniotic tissue plays an important role in epithelial differentiation at its native site, and then does the same when transplanted to the ocular surface.

II. Regulatory Background

The term "human cellular and tissue-based products" encompasses a wide range of products derived from the body and used for many medical purposes. In the past, most human tissue used in medicine consisted of body components such as skin, bone, corneas, and heart valves that were transplanted for replacement purposes, as well as semen and ova transplanted for reproductive purposes.

FDA's regulation of conventional tissues used for replacement purposes has focused on preventing the transmission of communicable diseases as authorized by the Public Heath Services Act ("PHS Act").[8] The agency has regulated human cellular and tissue-based products on a case-by-case basis. Tissues have been regulated as devices, biologics and drugs.

Where FDA has not classified tissue products as devices, biologics or drugs, the agency has regulated them under section 361 of the PHS Act, which authorizes regulations to prevent the spread of communicable diseases. Regulation under this authority has been light and focused. FDA requires donor screening and testing for hepatitis and human immunodeficiency viruses, as well as recordkeeping and availability of inspections.[9] However, beyond that, it has relied primarily on State regulation and voluntary accreditation systems.

III. FDA's Proposed New Regulatory Structure for Cellular and Tissue Based Products Clouds the Regulatory Status of Amniotic Membrane Tissue for Transplantation to the Ocular Surface

A. FDA's Proposed Approach Makes "Homologous Use" Central to Regulatory Status

In February 1997, FDA released two documents setting forth a proposed approach for the regulation of human tissue: "Reinventing the Regulation of Human Tissue," and "A Proposed Approach to the Regulation of Cellular and Tissue-Based

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[8] 42 U.S.C. § 262.

[9] 21 C.F.R. § 1270.

Products." These documents identified FDA's public health concerns regarding the use of human tissue, and outlined a framework for the regulation of both new and traditional tissue products. This included a hierarchy for when tissue would be regulated through the traditional channels for devices and biologics, and when it would be regulated separately as tissue under section 361 of the PHS Act.

FDA stated that the new framework was intended to focus on three goals: (1) preventing unwitting use of contaminated tissues with the potential for transmitting infectious diseases such as AIDS and hepatitis; (2) preventing improper handling or processing that might contaminate or damage tissues; (3) ensuring that clinical safety and effectiveness is demonstrated for tissues that are highly processed, are used for other than their normal function, are combined with non-tissue components, or are used for metabolic purposes.[10]

On May 14, 1998, FDA published in the *Federal Register* a proposed rule to require manufacturers of certain human cellular and tissue-based products to register with the agency and list their products.[11] On September 30, 1999, FDA published another proposed rule relating to human cellular and tissue-based products; this one regarding suitability determinations for donors.[12] These provisions would apply to all tissue products.

The proposed regulations provide that a human cellular or tissue-based product will be regulated as a drug, device or biologic if, *inter alia*, it is "promoted or labeled for any use other than a homologous use."[13] In addition to the registration and listing and donor screening requirements under section 361 of the PHS Act, products promoted or labeled for non-homologous uses will be subject to regulation under the Federal Food, Drug, and Cosmetic Act (FDCA) as drugs, devices and biologics, including premarket approval and good manufacturing practices. Thus, whether a particular application of a tissue product is considered a homologous use will have significant ramifications for how a manufacturer is regulated and how it may promote its products.

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10 "Proposed Approach" at 6.

11 63 Fed. Reg. 26744.

12 64 Fed. Reg. 52696.

13 Proposed 21 C.F.R. § 1271.15; 64 *Fed. Reg.* at 52720.

B. The Proposed Definition of Homologous Use Appears to Encompass Transplantation of Amniotic Membrane to the Cornea

In the proposed rule on registration, FDA proposed the following definition for homologous use:

> Homologous use means the use of a cellular or tissue-based product for replacement or supplementation and:
>
> (1) for structural tissue-based products, occurs when the tissue is used for the same basic function that it fulfills in its native state, in a location where such structural function normally occurs.[14]

This proposed definition strikes an appropriate balance, one consistent with the goals outlined in the Proposed Approach document. Homologous use would be one in which the tissue continues to do what it normally does in the body, in a part of the body where those functions take place. It limits homologous use of a tissue-based product to the same basic function as in its native state, but allows for transplant to different locations in the body.

Difficulties arise, however, in applying this formula to specific cases. The definition turns on the ambiguous term "basic function." In many instances, the details of what was a tissue's "basic function" in its native state, and whether it is repeated in the transplanted location, may be open to debate.

In the preamble to the proposed rule, FDA explained that the phrase "same basic function" refers to "what the tissue does from a biological/physiological point of view, or is capable of doing when in its native state."[15] Thus, the evaluation does not focus on a narrow comparison of the exact functions and interactions that occur at one location, but rather on what the tissue does from a larger biological/physiological point of view, *e.g.*, providing protection or fostering cell regeneration. Moreover, FDA invites consideration of what the tissue is "capable of doing" when in its native state, *i.e.*, if it could promote cell growth and healing in its native state, and then actually does so in the transplanted location, that would be a homologous use as well. For example, the agency stated that

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[14] Proposed 21 C.F.R. § 1271.3(d); 63 *Fed. Reg.* 26754.

[15] 63 *Fed. Reg.* at 26749.

a homologous use would be "to replace an analogous structural tissue that has been damaged or otherwise does not function adequately."[16]

To illustrate further FDA's understanding of "same basic function" and homologous use, the preamble gives specific examples of homologous functions for structural tissue. These include:

- bone allograft from a long bone labeled for use in a vertebra;
- skin allograft obtained from the arm but labeled for use as a skin graft on the face;
- pericardium, a structural covering of the heart, labeled for use as a structural membranous covering for the brain; and
- human heart valves labeled for use as heart valves.[17]

It then provides a single example of non-homologous uses for structural tissue: cartilage labeled for placement under the sub-mucosal layer of the urinary bladder to change the angle of the ureter and thereby prevent backflow of urine from the bladder.[18]

Transplantation of amniotic membrane tissue to the cornea is consistent with this understanding of homologous use. FDA's examples expressly anticipate the transplant of membrane tissue from one location in the body to another. FDA states that it would consider the use of a structural membranous covering of the heart to fulfill a homologous function when it is labeled for use as a structural membranous covering of the brain. Clearly the membrane does not perform the identical function -- protecting the same structures, supporting the same cells -- over the brain as it does over the heart. However, the basic function, from a biological and physiological standpoint, is the same. This is equally true in the case of the amniotic membrane transplanted to the ocular surface. This is consistent with the transplantation of amniotic membrane tissue to an injured cornea, where the membrane covers the epithelial layer and promotes the growth and regeneration of cells that would occur there in the absence of injury.

The example given for non-homologous use is instructive by way of contrast. The basic function of cartilage is to provide structural support. The use described, to angle the ureter to prevent backflow, involves structural support, but in a location in

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[16] Id.

[17] Id.

[18] Id.

which such structural support does not normally exist. This is not the case for amniotic membrane transplanted to the ocular surface. It acts as a protective layer, and fosters cell regeneration, just as the stem cells of the epithelial layer would in the absence of injury. The transplanted amniotic membrane -- which, as described above, consists of structural components (type IV collagen, laminin, and type VII collagen) similar to those of the ocular surface -- enables these functions to proceed, just as it does in its native state.

C. The History of the Rule Clouds FDA's Intent Regarding Amniotic Tissue

1. FDA's Proposed Approach Document Listed Transplantation of Amniotic Membrane as Non-Homologous

While the transplant of amniotic membrane tissue to the ocular surface is consistent with the definition of homologous use as explained in the preamble to the proposed rule, the history of FDA's policy in this area raises some questions. In the Proposed Approach document published in 1997, FDA defined homologous use in terms virtually identical to the proposed rule -- "to replace an analogous structural tissue that has been damaged or otherwise does not function adequately." Conversely, FDA stated that a non-homologous use of structural tissue would be use for a purpose different from that which it fulfills in its native state, or in a location of the body where such structural function does not normally occur.

FDA then listed the same specific examples of homologous uses for structural tissue as appeared in the proposed rule: bone allograft from a long bone used in a vertebra; skin allograft obtained from the arm but used as a skin graft on the face; pericardium, a structural covering of the heart, used as a structural covering of the brain; and human heart valves.[19]

FDA provided two examples of non-homologous uses for structural tissue: cartilage placed under the sub-mucosal layer of the urinary bladder; and "amniotic membrane used for wound healing on the cornea." FDA stated that the use of the amniotic membrane in this instance would be non-homologous because it would be intended to heal a damaged corneal epithelium by growing new corneal epithelial cells, a function it does not normally perform in utero.

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[19] "Proposed Approach" at 18. FDA listed one additional example of homologous use -- human dura matter, a fibrous covering of the brain, used as a covering -- which does not appear in the proposed rule.

2. FDA Appears to Have Since Recognized Transplantation of Amniotic Membrane to the Cornea as Homologous

In the Proposed Approach document, FDA appeared to have reconsidered the actual use and functions of amniotic membranes transplanted to the ocular surface. As described more fully above, the amniotic membrane does in fact perform the same basic function on the corneal or conjunctival epithelium as it does when covering the amniotic sac -- protection from insult, and rapid restoration of tissue architecture without acute inflammatory reaction and scarring -- albeit in a different location. While amniotic membrane does not grow new corneal or conjunctival epithelial cells while it is located in utero, it does foster regeneration of epithelial cells at that site. It does the same when transplanted to the ocular surface, with the result that new corneal or conjunctival epithelial cells are grown, because those are the cells present at the site. This is consistent with FDA's core example of a homologous use -- replacing an analogous structural tissue that has been damaged or otherwise does not function adequately. One cannot logically maintain both that homologous use may encompass transplantation to a different site in the body and that transplantation is non-homologous when the tissue interacts with different cells from those with which it interacted at its native site.

When the policy reached the rulemaking stage, the drafters of the proposed rule appear to have recognized this distinction. The proposed definition of homologous use is the same as that of the proposed approach, *i.e.*, that "the tissue is used for the same basic function that it fulfills in its native state." Conspicuously absent from the specific examples of homologous and non-homologous use -- which is otherwise virtually identical to that which appeared in the proposed approach -- is the use of amniotic membrane for wound healing on the cornea. This implies that FDA reconsidered its earlier position, and recognized that this use is a homologous one. Indeed, it appears to have applied refined criteria that it presented in the proposed rule, by considering what the tissue does from a biological/physiological point of view, rather than a narrow comparison of locations. This is consistent with the function that the transplanted membrane performs and with the makeup of its structural components.

IV. FDA Should Clarify its Position and State That Transplantation of Amniotic Membrane to the Cornea as Homologous

FDA's apparent acceptance of the position that transplantation of amniotic membrane to the cornea or conjunctiva can be a homologous use is consistent with the broader principles set forth in the proposed rule. Moreover, it is more consistent with the modified list of examples given in the proposed rule. FDA should state explicitly that

this is its policy or identify amniotic membrane as an example of homologous use in the preamble, the discussion of comments received, or in the rule itself.

This approach is consistent with the three principles identified in the Proposed Approach as underlying FDA's framework for regulation. The amniotic membranes supplied by Bio-Tissue are carefully screened and guarded against the risk of contamination and potential transmission of infectious diseases. This is necessary to comply not only with professional practice, but also the requirements of state certification and the donor screening and testing procedures that FDA will put into place in the final rule. Moreover, Bio-Tissue has in place careful procedures to prevent improper handling or processing that might contaminate or damage tissues, consistent with the standards of the AATB, as well as those of the New York Department of Health, Division of Laboratory Quality Certification.

With regard to the final factor identified in the Proposed Approach, clinical demonstration for safety and effectiveness is not necessary because the tissues are not "highly processed, are used for other than their normal function, are combined with non-tissue components, or are used for metabolic purposes." Bio-Tissue performs the absolute minimum of processing necessary on the amniotic membranes, essentially only those steps required to store and preserve them until the time of transplant. The tissues are used for their normal function, the protection and the promotion of cell regeneration, as discussed above. The transplanted membranes are not combined with non-tissue components, and they are not used for metabolic purposes. Thus, they are appropriately regulated as tissue intended for a homologous use under section 361 of the PHS Act, rather than the more demanding premarket approval requirements of the Food, Drug and Cosmetic Act. The unique properties of the amniotic membrane and the ocular surface, and the important structural basis for the similarities of function discussed in 1.C. above, make this a unique application. Recognition by FDA will not open a floodgate of overly broad interpretations of "homologous use."

While Bio-Tissue is not required to demonstrate the clinical safety and effectiveness of an amniotic membrane intended for a homologous use, there is a growing body of published medical literature and research supporting its safety and effectiveness for this intended use. Numerous papers have been published on transplantation of amniotic membrane for use in ocular surface reconstruction. A symposium conducted at the Bascom Palmer Eye Institute at the University of Miami School of Medicine's Fourth Ocular Surface and Tear Conference on May 14, 1999 presented the research of more than 20 investigators on hundreds of patients.[20] A list

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[20] The symposium was supported, in part, by an unrestricted educational grant from Bio-Tissue, Inc.

of references to published articles is attached at TAB 1. A review of the literature by Scheffer Tseng, M.D., Ph.D., is attached at TAB 2. Abstracts from the presentations at the Bascom Palmer Eye Institute symposium is attached at TAB 3.

V. Conclusion

Bio-Tissue respectfully requests that FDA state affirmatively in the final rule -- in the preamble, the discussion of comments received, or in the rule itself -- that transplantation of amniotic membrane to the ocular surface is a homologous use.